

Appl. No. : 09/919,349
Filed : July 31, 2001

REMARKS

Claims 1, 5, 6, 11, 16, and 21 have been amended. As a result, Claims 1-25 remain pending in the present application. Support for the amendments is found in the specification and claims as filed. Accordingly, the amendments do not constitute the addition of new matter. Reconsideration of the application in view of the foregoing amendments and following comments is respectfully requested.

Rejections under 35 U.S.C. § 112

The Examiner rejected Claims 1-25 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner rejected Claims 1, 6, 11, 16, and 21 for reciting the term "COX." Claims 1, 6, 11, 16, and 21 have been amended to recite "cyclooxygenase-2 (COX-2)."

The Examiner rejected Claim 1 for reciting the term "derivative." Claim 1 has been amended to remove the term "derivative."

The Examiner rejected Claims 2-5, 7-10, 12-15, 16-20, and 22-25 for capitalizing the "C" in "claim." In a telephone conversation on May 22, 2003, the Examiner indicated that replacing the capital "C" with a small "c" was simply a suggestion and that she would not reject the claims on this basis again.

The Examiner rejected Claims 1, 6, 11, 16, and 21 for reciting the term "minimal effect." Claims 1, 6, 11, 16, and 21 have been amended to remove the term "minimal effect."

The Examiner rejected Claim 5 for misspelling "chondroitin." Claim 5 has been amended to correct the misspelling.

The Examiner rejected Claim 6 for misspelling "melapomdin A." Claim 6 has been amended to correct the misspelling.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 U.S.C. § 112, second paragraph.

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Rejections under 35 U.S.C. § 103

The Examiner rejected Claims 1-4, 6-9, 11-14, 16-19 and 21-24 under 35 U.S.C. § 103(a) as being unpatentable over Tao et al. in view of Hwang, et al. The Examiner further rejected Claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Tao and Hwang in view of Bath et al., Petrus, Henderson, et al., Takamiya et al., and Hesch. For both rejections, the Examiner stated that "Applicants' invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients." As discussed below, specific proportions of the synergistic ingredients are now recited in the claim. Accordingly, the claims encompass only mixtures that do exhibit unexpected results.

According to M.P.E.P. 716.02, a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness of the claims at issue. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness.

The combination of diterpene triepoxide lactone species and sesquiterpene lactone species in a ratio range of between 100:1 and 1:100 was shown to have a synergistic effect on inhibition of PGE₂ biosynthesis. In the enclosed Declaration under 37 C.F.R. § 1.132, experimental results demonstrate a synergism of diterpene triepoxide lactone species, as triptolide, and sesquiterpene lactone species, as parthenolide, for an increased inhibitory effect.

As stated in paragraph 11 of the Declaration, all of the ratios of diterpene triepoxide lactone species, as triptolide, and sesquiterpene lactone species, as parthenolide, from 100:1 to 1:100 were found to be as synergistic by the Combination Index (CI) parameter. The low values for CI indicate extremely strong synergy between parthenolide and triptolide within these ratios. Unexpectedly, only one percent of either parthenolide or triptolide in the combination of the two agents produces an inhibition of PGE₂ biosynthesis greater than either material alone at the respective concentration. Also, unexpectedly, this synergy exists over the entire dose-response range of the combinations as indicated by the mean CI values less than one. Even more unexpectedly, CI's are greater than 1.0 at the extremes of the ratios, 1000:1, 500:1, 1:500 and

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1:1000, indicating antagonism. Thus, at least the entire range of ratios for parthenolide:triptolide combinations between 100:1 and 1:100 exhibits synergism. This finding is unexpected. Accordingly, Claim 1 has been amended to recite the ratios between 100:1 to 1:100. Support for this amendment can be found at page 18, lines 19-21 where the preferred amounts of each of the diterpene triepoxide lactone and sesquiterpene lactone is disclosed to be 0.01 to 1 wt. %. The 100:1 to 1:100 ratio can be readily derived from the preferred amounts.

According to M.P.E.P. 716.02(a), presence of a property not possessed by the prior art is evidence of nonobviousness. The finding of synergistic inhibitory effect from the combination of a diterpene triepoxide lactone species and a sesquiterpene lactone species is unexpected. As such, Claims 1-25 which recite this combination of ingredients are nonobvious and patentable.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

Double Patenting

The Examiner provisionally rejected Claims 1-25 under the doctrine of double-patenting as being unpatentable over Claim 1-3, 6-14, 16-23, 25-32, and 34-38 in copending Application No. 09/919,506. In accordance with 37 CFR 1.321, Applicants have filed herewith a terminal disclaimer to overcome this provisional rejection. Applicants therefore respectfully request that the Examiner withdraw the rejection of Claims 1-25 on the ground of double patenting.

CONCLUSION

In view of the foregoing amendments and comments, it is respectfully submitted that the present application is fully in condition for allowance, and such action is earnestly solicited.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped

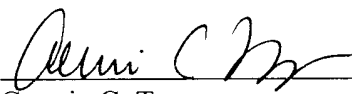
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issues remain or if any issues require clarification, the Examiner is invited to call the undersigned in order to resolve such issue promptly.

Respectfully submitted,

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Dated: September 2, 2003

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